REMARKS

Claims 97-112 have been canceled without prejudice or disclaimer. Claims 113-120 have been added and therefore are pending in the present application. Claims 113-122 are supported by claims 97-112.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 105-112 under 35 U.S.C. 112

The Office maintained the rejection of claims 105-112 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Office stated:

> [T]he specification ... fails to exemplify or describe the practice of the method of selection of the new claim 105, and the dependent claims 106-112 ... where they fail to introduce processes absent from claim 105, because the method set forth in claim 105 is not a method of selection that the specification describes.

Claims 105-112 have been rewritten as claims 117-120 to address this rejection. Applicants therefore submit that this rejection has been overcome.

II. The Rejection of Claims 97-112 under 35 U.S.C. 112

Claims 97-112 are rejected under 35 U.S.C. 112 "because the specification is not enabling for a method of selecting a less immunogenic enzyme or medicinal protein by random alteration of the amino acid sequence or a reference protein to produce selectable variants that may or may not be less immunogenic. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." This rejection is respectfully traversed.

It is well settled that "[t]he first paragraph of section 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). Moreover, "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance

with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 USPQ at 369.

"The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed ..." *Ex parte Jackson*, 217 U.S.P.Q. 804 (Bd. Pat. App. 1982).

It is also well settled that an assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974). See also *U.S. v. Telectronics*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974); *Ex parte Hitzeman*, 9 U.S.P.Q.2d 1821 (BPAI 1988).

Applicants submit that based on the above legal standards, the specification enables the claimed inventions.

The present invention relates to methods for selecting a variant enzyme of a reference enzyme, wherein the variant enzyme causes a lower immunogenic response in a mammal than the reference enzyme and has an altered amino acid sequence of one or more epitopes of the reference enzyme.

The specification contains an extensive disclosure of how to select the variant enzymes. For example, the specification at pages 6-8 discloses numerous techniques which can be used for mapping an epitope of an enzyme such as the production of antibodies which can recognize one or more epitopes. In addition, the specification describes assays which are able to identify enzyme variants with a changed antibody binding capacity. These techniques are well known and routine for persons of ordinary skill in the art. There is no evidence to the contrary.

Moreover, assays for determining enzyme activity are well known in the art. These techniques are well known and routine for persons of ordinary skill in the art. Again, there is no evidence to the contrary.

In an effort to meet his burden that the claims are not enabled, the Examiner theorizes that because "there is no resolution yet available of the tertiary structure of a ggeneric reference enzyme or medicinal protein." This is respectfully traversed.

As described in the specification, the tertiary structure of an enzyme is not required for mapping an epitope of an enzyme. An epitope can be mapped using the techniques described in the specification. Based on Applicants' disclosure, it would be routine for one of ordinary skill in the art to produce an enzyme variant having enzyme activity and a lower immunogenic response in a mammal than the reference enzyme.

We draw the Examiner's attention to *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976). In *Angstadt*, the claimed process of preparing hydroperoxides used a metal salt complex as a catalyst. The specification disclosed catalysts that worked and some that gave little or no yield of hydroperoxides. The claims were rejected for lack of enablement, specifically as requiring undue experimentation to find useful catalysts. This rejection was reversed by the CCPA.

In holding that the claims did satisfy 35 U.S.C. 112, the Court observed, 190 U.S.P.Q. at 218:

> We cannot agree with the board that appellants' disclosure is not sufficient to enable one of ordinary skill in the art to practice the invention without undue experimentation. We note that many chemical processes, and catalytic processes particularly, are unpredictable, [citation omitted] and that the scope of enablement varies inversely with the degree of unpredictability involved, [citation omitted]. That this particular process is unpredictable is demonstrated further by appellants in their specification. Appellants have disclosed forty examples; one of these examples yields no hydroperoxides in the final product. Also, appellants have expressly indicated in their specification that some of these organometallic complex catalysts 'yield *** no hydroperoxides in the final product.'
>
> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with 'thousands' of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid 'literal' infringement of such claims by merely finding another analogous catalyst complex which could be used in 'forming hydroperoxides.'

This admonition applies with equal force to the present application, which discloses numerous lipases that will work and discloses numerous Examples illustrating the present

process, but does not characterize any lipase as inactive. To require more would fly in the face of the *Angstadt* holding.

The Court, 190 U.S.P.Q. at 218, recognized that some experimentation might be necessary for the skilled worker to select non-exemplified catalysts for use:

> Appellants have, in effect, provided those skilled in this art with a large but finite list of transition metal salts from which to choose in preparing such a complex catalyst. Appellants have actually carried out 40 runs using various transition metal salts and hexaalkylphosphoramides. If one skilled in this art wished to make and use a transition metal salt other than those disclosed in appellants' 40 runs, he would merely read appellants' specification for directions how to make and use the catalyst complex to oxidize the alkylaromatic hydrocarbons, and could then determine whether hydroperoxides are, in fact, formed. The process discovered by appellants is not complicated, and there is no indication that special equipment or unusual reaction conditions must be provided when practicing the invention. One skilled in this art would merely have to substitute the correct mass of a transition metal salt for the transition metal salts disclosed in appellants' 40 runs. Thus, we have no basis for concluding that persons skilled in this art, armed with the specification and its 40 working examples, would not easily be able to determine which catalyst complexes within the scope of the claims work to produce hydroperoxides and which do not.

However, while some experimentation might be necessary, as long as the experimentation was not "undue experimentation," the claims would not violate 35 U.S.C. 112, *Angstadt*, Id:

> Since appellants have supplied the list of catalysts and have taught how to make and how to use them, we believe that the experimentation required to determine which catalysts will produce hydroperoxides would not be undue and certainly would not 'require ingenuity beyond that to be expected of one of ordinary skill in the art.' (Emphasis added).

As in *Angstadt*, the present application identifies a large number of specific lipases that can be used as catalysts at page 8, line 13 to page 10, line 3. The Examples illustrate how the lipase catalyst is used. While some experimentation might be necessary to determine whether a non-exemplified lipase could in fact be used, such experimentation would require carrying out a simple process without special equipment or unusual reaction conditions, as in *Angstadt*. This experimentation, if required, "would not be undue and certainly would not 'require ingenuity beyond that expected of one of ordinary skill in the art.'" (*Angstadt*, 190 U.S.P.Q. at 218). Certainly, there is no evidence of record to the contrary.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 97-112 under 35 U.S.C. 112

Claims 97-112 are rejected under 35 U.S.C. 112 as being indefinite. The Office provided several grounds for this rejection.

Claims 97-112 have been rewritten as claims 113-122 to address this rejection. Applicants therefore submit that this rejection has been overcome.

IV. The Rejection of Claims 97-112 under 35 U.S.C. 103

Claims 97-112 are rejected under 35 U.S.C. 103 as being unpatentable over Ladner et al. (U.S. Patent No. 5,223,409). Specifically, the Office stated that:

> The new claims do not describe methods requiring epitope mapping of integral enzymes or medicinal proteins, in accord with Applicant's arguments, thus do not avoid the teachings of Ladner et al....

This rejection is respectfully traversed.

Step (c) of both independent claims 113 and 117 recite "mapping one or more epitopes of the reference enzyme with immunological techniques." Thus, the Office is incorrect that the claims do not describe methods requiring epitope mapping of integral enzymes or medicinal proteins.

As explained in the previous response, Ladner et al. disclose a method of producing phage libraries of variants by controlled random mutagenesis ("variegation") and then selecting phages bearing those variants that do not bind to a target. The Ladner et al. method involves ontrolling the variegation to target amino acid residues located on the surface of streptokinase and raising an antibody against streptokinase for attachment to a column. The variants are selected by being placed in the antibody column and phages bearing those variants that do not bind to the column are collected and cultured.

However, Ladner et al. never map an epitope, i.e., Ladner et al. never identify the amino acids that form an epitope. Instead, Ladner et al. select variants that do not bind to the antibody column or which bind weakly when eluted in a salt gradient. Although some of these variants may have a mutation of an amino acid that forms an epitope, Ladner et al. do not disclose or suggest which mutations belong to an epitope or which mutations belong to the same epitope. For example, a variant selected by the method of Ladner et al. might contain five amino acid

substitutions, three of which are part of epitopes, and two of which are due to the randomness of the variegated library design. Ladner et al. do not suggest any method of determining which of the five mutations are mutations of an epitope and which are not. Furthermore, Ladner et al. do not suggest any method of determining whether the three mutations that are mutations of an epitope are mutations of the same or different epitope.

Moreover, Ladner et al. state that, "Destroying binding frequently requires only that a single amino acid in the binding interface be changed." This indicates that Ladner et al. are not interested in mapping any epitope.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

V. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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